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GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

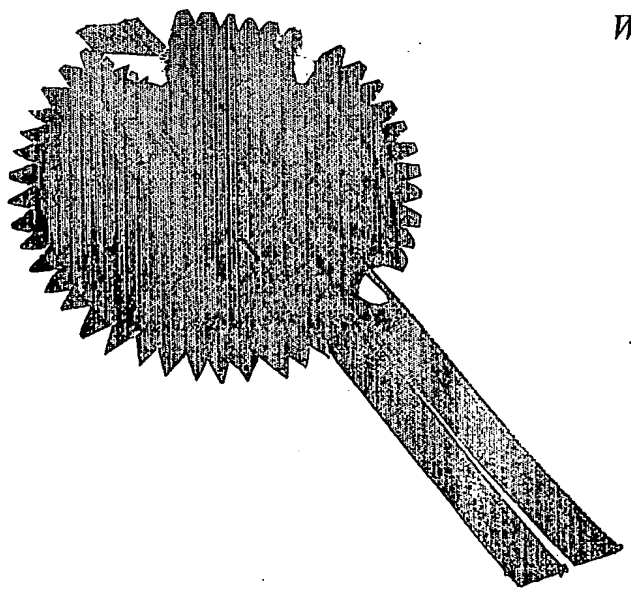
REC'D 03 JUN 2005
WIPO PCT

IB/05/512

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Provisional Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***307/Del/2004*** *dated* ***27th February 2004.***

Witness my hand this 2nd day of May 2005.

(S.K. PANGASA)
Assistant Controller of Patents & Designs



0307 - 04

27 FEB 2004

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR PREPARATION OF BENZOISOTHIAZOLE DERIVATIVES OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR
b. MOHAN PRASAD
c. MAHAVIR SINGH KHANNA
d. SEEMA AHUJA

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:

We, YATENDRA KUMAR, MOHAN PRASAD, MAHAVIR SINGH KHANNA, SEEMA AHUJA of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(YATENDRA KUMAR)

b.

(MOHAN PRASAD)

c.

(MAHAVIR SINGH KHANNA)

d.

(SEEMA AHUJA)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Provisional Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.**3,000**/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on HDFC Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this **26TH** day of **February, 2004.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2 0307/04

27 FEB 2004

The Patents Act, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

PROCESS FOR PREPARATION OF BENZOISOTHIAZOLE PIPERAZINE DERIVATIVES OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for preparation of benzoisothiazole piperazine derivative or a pharmaceutically acceptable salt thereof. The present invention also relates to substantially pure benzoisothiazole piperazine derivative or a pharmaceutically acceptable salt thereof.

In particularly the present invention relates to a process for preparation of ziprasidone or pharmaceutically acceptable salt thereof. In addition the present invention also relates to substantially pure ziprasidone or a pharmaceutically acceptable salt thereof.

Ziprasidone hydrochloride of Formula IA as shown in the accompanied drawing, is chemically hydrochloride salt of 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl] ethyl]-6-chloro-1,3-dihydro-2*H* -indol-2-one. It is indicated for the treatment of schizophrenia.

US Patent No. 4,831,031 in Example 16 provides an analogous process for preparation of Ziprasidone hydrochloride which involves refluxing N-(1,2-benzisothiazol-3-yl)piperazine with 5-(2-chloroethyl)-6-chloro-oxindole in methyl isobutyl ketone in presence of sodium iodide and sodium carbonate for about 40 hours followed by column chromatographic purification of the product to get ziprasidone base which is dissolved in methylene chloride and treated with ethereal hydrogen chloride to get ziprasidone hydrochloride salt.

US Patent No. 5,312,925 provides another process for preparation of ziprasidone hydrochloride which involves heating to reflux a mixture of 5-(2-chloroethyl)-6-chloro-oxindole and 1-(1,2-benzisothiazol-3-yl) piperazine in aqueous sodium carbonate for 14 hours, followed by cooling to 20°C and filtration. The wet product is re-slurried in isopropyl alcohol and filtered, washed with fresh isopropyl alcohol followed by drying under vacuum to get ziprasidone base. The base is then treated with aqueous hydrochloric acid in presence of water at a temperature of about 60-65°C for 3 to 24 hours, followed by filtration, washing with water and drying under vacuum to get ziprasidone hydrochloride.

US Patent No. 5,206,366 and 5,338,846 provide process for preparation of ziprasidone base which involves heating to reflux a mixture of 5-(2-chloroethyl)-6-chloro-oxindole and 1-(1,2-benzisothiazol-3-yl) piperazine in aqueous sodium carbonate for 13 hours followed by cooling to 25°C and filtration. The product is re-slurried in isopropyl alcohol twice and

then filtered and dried under vacuum. The dried product is recrystallized from tetrahydrofuran to get ziprasidone base having a purity of 99.7% measured by HPLC.

US Patent No. 6,150,366 provides a process for preparation of ziprasidone hydrochloride from double recrystallized ziprasidone base having a purity of about 99.7% by HPLC. The process involves refluxing a slurry of ziprasidone base in tetrahydrofuran and water to get clear solution followed by addition of aqueous hydrochloric acid solution at 60-62°C in two lots, cooling the mixture to 13°C to complete crystallization of ziprasidone hydrochloride. The product is filtered and washed with fresh cold tetrahydrofuran.

The present inventors have surprisingly found that ziprasidone base of Formula IB can be prepared by refluxing a mixture of compound of Formula II, wherein L is a leaving group and 1-(1,2-benzisothiazol-3-yl) piperazine of Formula III in water without adding any base or a catalyst. The process requires about 5-10 hours for completion which is by far the lowest reaction time when compared with the prior-art processes. The crude ziprasidone base obtained has purity above 97%, which again is the highest among the prior-art processes.

In the context of present invention the term "substantially pure ziprasidone hydrochloride refers to ziprasidone hydrochloride or a crystalline form, solvate, hydrate thereof having a purity above 99.8% wherein total impurities are less than 0.2% when determined by HPLC. More preferably substantially pure ziprasidone hydrochloride has purity greater than 99.9% wherein total impurities less than 0.1% by HPLC.

The term "substantially pure ziprasidone base" refers to ziprasidone base having purity above 99.75% wherein total impurities are less than 0.25% when determined by HPLC. More preferably the substantially pure ziprasidone base has purity above 99.9% wherein total impurities are less than 0.1% by HPLC.

A first aspect of the invention provides a process for preparation of ziprasidone base of Formula IB wherein the said process comprises of

a) treating a aqueous mixture of compound of Formula II, wherein L is a leaving group and 1-(1,2-benzisothiazol-3-yl)piperazine of Formula III in absence of a base,

b) heating the resultant mixture from 60°C to reflux,

c) isolating ziprasidone base of Formula IB from the reaction mass,

An aqueous mixture of compound of Formula II, wherein L is a leaving group, and 1-(1,2-benzisothiazol-3-yl) piperazine of Formula III is heated optionally in presence of an organic solvent at a temperature of about 60°C to reflux temperature in absence of a base. The reaction mass after completion of reaction (as monitored by HPLC) is filtered at a temperature of about 40°C to about 100°C and the wet product obtained is re-slurried from de-ionized water at room temperature to 100°C. After filtering the product, the wet cake can be suspended in isopropyl alcohol, heated to reflux and then cooled and filtered to get ziprasidone base having purity above 97% by HPLC.

The leaving group L present in compound of Formula II is conventional leaving group known to a person of ordinary skills in art. The leaving group for example can be selected from a group comprising of chloro, bromo, iodo, mesyloxy, tosyloxy or acetyloxy and the like.

The organic solvent can be selected from a group comprising of alcohols, ketones, polar aprotic solvents, esters or mixtures thereof. The organic solvent comprises of methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol, acetone, ethyl methyl ketone, tetrahydrofuran, N,N-dimethylacetamide, N,N-dimethylformamide, acetonitrile, 1,4-dioxane, N-methylpyrrolidone, ethyl acetate or mixtures thereof.

A second aspect of the invention provides a process for preparation of substantially pure ziprasidone base wherein the said process comprises of

a) suspending ziprasidone in an organic solvent

b) heating the resultant mass to 40°C to reflux temperature

c) adding water to the reaction mass and if required heating to get clear solution

d) optionally concentrating the clear solution

e) cooling the reaction mass and

f) isolating substantially pure ziprasidone base.

Ziprasidone base obtained in first aspect of the invention is suspended in an organic solvent and the resultant mass is heated to about 45°C or upto reflux temperature. To the

reaction mass water is added and if required can be heated further to get clear solution. The clear solution can be optionally concentrated by conventional means and cooled to desired temperature. The precipitated solid is then isolated by conventional means and dried suitably to get substantially pure ziprasidone base.

The organic solvent comprises of water miscible organic solvents selected from a group comprising of tetrahydrofuran, methanol, ethanol, n-propanol, isopropanol, acetone, acetonitrile or mixtures thereof.

A third aspect of the invention provides a process for preparation of substantially pure ziprasidone base wherein the said process comprises of

a) suspending ziprasidone in a mixed organic solvent
b) heating the resultant mass to 40°C to reflux temperature to get clear solution
c) optionally concentrating the clear solution
d) cooling the reaction mass and
e) isolating substantially pure ziprasidone base.

Ziprasidone base obtained in first aspect of the invention is suspended in an organic solvent and the resultant mass is heated to about 45°C or upto reflux temperature to get a clear solution. The solution can then be optionally concentrated by conventional means and cooled suitably. The resultant product is then isolated by conventional means and dried to get substantially pure ziprasidone base.

The mixed organic solvent comprises of mixture of two or more organic solvents selected from a group comprising lower alkanols, chlorinated hydrocarbons or polar aprotic solvents or mixtures thereof. The organic solvents comprises of methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, acetone, acetonitrile, methylene chloride, chloroform, ethylene chloride.

A fourth aspect of the invention provides substantially pure ziprasidone base having purity above 99.75% wherein total impurities are less than 0.25% when determined by HPLC. More preferably substantially pure ziprasidone base has purity above 99.9% wherein total impurities are less than 0.1% when determined by HPLC.

A fifth aspect of the invention provides a process for preparation of ziprasidone hydrochloride of Formula IA wherein the said process comprises of

a) treating a aqueous mixture of compound of Formula II wherein L is a leaving group and 1-(1,2-benzisothiazol-3-yl) piperazine of Formula III in absence of a base,
b) heating the resultant mixture from 50°C to reflux,
c) isolating ziprasidone base from the reaction mass,
d) converting the ziprasidone base to ziprasidone hydrochloride by treating it with hydrogen chloride
e) isolating ziprasidone hydrochloride of Formula IA from the reaction mass.

Ziprasidone base is treated with hydrogen chloride in presence of an organic solvent at a temperature of about 50°C to reflux. Ziprasidone hydrochloride can be isolated from the reaction mass by conventional techniques such as filtration, decantation, centrifugation and the like. The wet product is washed with a suitable organic solvent such as isopropyl alcohol, diethyl ether or acetone and dried conventionally.

The organic solvent can be selected from a group comprising of chlorinated hydrocarbons, aromatic hydrocarbons, polar aprotic solvents, ethers, ketones, lower alcohols or mixtures thereof. The organic solvent comprises of methylene chloride, chloroform, ethylene chloride, toluene, xylene, substituted toluenes, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, 1,4-dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, acetone, ethyl methyl ketone, diisobutyl ketone, methyl isobutyl ketone, methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol or mixtures thereof.

Hydrogen chloride can be added as a solution in a suitable organic solvent already mentioned above or in the form of gas, which is purged through the mixture of ziprasidone base in an organic solvent. Aqueous solution of hydrogen chloride can also be conveniently used.

A sixth aspect of the present invention provides a process for the preparation of substantially pure ziprasidone hydrochloride wherein the said process comprises of

a) treating substantially pure ziprasidone base with hydrogen chloride in presence of an organic solvent

b) isolating substantially pure ziprasidone hydrochloride from the reaction mass.

Substantially pure ziprasidone base is suspended or dissolved in an organic solvent and the resultant mass is treated with hydrogen chloride.

The organic solvent can be selected from a group comprising of chlorinated hydrocarbons, aromatic hydrocarbons, polar aprotic solvents, ethers, ketones, lower alcohols or mixtures thereof. The organic solvent comprises of methylene chloride, chloroform, ethylene chloride, toluene, xylene, substituted toluenes, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, 1,4-dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, acetone, ethyl methyl ketone, diisobutyl ketone, methyl isobutyl ketone, methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol or mixtures thereof.

Hydrogen chloride can be added as a solution in a suitable organic solvent already mentioned above or in the form of gas, which is purged through the mixture of ziprasidone base in an organic solvent. Aqueous solution of hydrogen chloride can also be conveniently used.

Substantially pure ziprasidone hydrochloride can be isolated from the reaction mass by conventional techniques such as filtration, decantation, centrifugation and the like. The wet product is washed with a suitable organic solvent such as isopropyl alcohol, diethyl ether or acetone and dried conventionally.

A seventh aspect of the invention provides substantially pure ziprasidone hydrochloride having purity above 99.8% wherein total impurities less than 0.2% when determined by HPLC. More preferably substantially pure ziprasidone hydrochloride has purity above 99.9% wherein total impurities are less than 0.1% when determined by HPLC.

An eighth aspect of the invention provides pharmaceutical compositions comprising substantially pure ziprasidone base or substantially pure ziprasidone hydrochloride as active ingredient along with a pharmaceutically acceptable carriers/excipients/diluents.

A ninth aspect of the present invention provides method of treating schizophrenia which comprises of administering to a mammal in need thereof a therapeutically effective amount of substantially pure ziprasidone base or substantially pure ziprasidone hydrochloride.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLE 1

PREPARATION OF ZIPRASIDONE BASE

To de-ionized water (2.0 Lit) was added 5-(2-chloroethyl)-6-chloro-oxindole (100 g) and 1-(1,2-benzisothiazol-3-yl) piperazine (210 g) at 30-35°C. The mixture was slowly heated under stirring to 98-100°C over 60-80 minutes. The resultant mass was stirred for 10-15 hours at 98-100°C. After completion of reaction as monitored by HPLC, the suspended solid material was filtered at 98-100°C. The wet cake obtained was suspended in to de-ionized water (2.0 Lit) and heated to 90-95°C and further maintained for 30 minutes. The solid suspension was filtered at 90-95°C. The wet cake was further added to isopropyl alcohol (1.5 Lit) and stirred for 2 hours at 30-35°C. The solids were filtered and washed with isopropyl alcohol (500 ml) and dried under vacuum at 50-55°C for 7-8 hours till moisture content is not more than 1.0% w/w.

Yield: 145 g (82%)
Purity: greater than 97.0 % by HPLC

EXAMPLE 2

PREPARATION OF ZIPRASIDONE BASE

To de-ionized water (1.5 Lit) was added 5-(2-bromoethyl)-6-chloro-oxindole (75 g) and 1-(1,2-benzisothiazol-3-yl) piperazine (132 g) at 30-35°C. The mixture was slowly heated under stirring to 98-100°C over 60-80 minutes. The resultant mass was stirred for 4-5 hours at 98-100°C. After completion of reaction as monitored by HPLC, the suspended solid material was filtered at 98-100°C. The wet cake obtained was suspended in to de-

ionized water (1.5 Lit) and heated to 90-95°C and further maintained for 30 minutes. The solid suspension was filtered at 90-95°C. The wet cake was further added to isopropyl alcohol (1.5 Lit) and the resultant mass was heated to reflux and maintained at reflux for 1 hour. The mass was further cooled to 30-35°C and stirred for 2 hours at 30-35°C. The solids were filtered and washed with isopropyl alcohol (75 ml) and dried under vacuum at 50-55°C for 7-8 hours till moisture content is not more than 1.0% w/w.

Yield: 96.5 g (85%)
Purity: greater than 97.0 % by HPLC

EXAMPLE 3

PREPARATION OF SUBSTANTIALLY PURE ZIPRASIDONE BASE

To de-ionized water (1.5 Lit) was added 5-(2-bromoethyl)-6-chloro-oxindole (75 g) and 1-(1,2-benzisothiazol-3-yl) piperazine (132 g) at 30-35°C. The mixture was slowly heated under stirring to 98-100°C over 60-80 minutes. The resultant mass was stirred for 4-5 hours at 98-100°C. After completion of reaction as monitored by HPLC, the suspended solid material was filtered at 98-100°C. The wet cake obtained was suspended in to de-ionized water (1.5 Lit) and heated to 90-95°C and further maintained for 30 minutes. The solid suspension was filtered at 90-95°C. The wet cake was further added to isopropyl alcohol (1.5 Lit) and the resultant mass was heated to reflux and maintained at reflux for 1 hour. The mass was further cooled to 30-35°C and stirred for 2 hours at 30-35°C. The solids were filtered and washed with isopropyl alcohol (75 ml) and dried under vacuum at 50-55°C for 7-8 hours till moisture content is not more than 1.0% w/w.

The product obtained was suspended in tetrahydrofuran (2.37 Lit) and heated to reflux (65-67°C. Maintained the resultant mass under reflux for 10-15 minutes. Added de-ionized water (190 ml) at 65-67°C and further stirred under reflux at 65-67°C for 15-20 minutes to get clear solution. Added activated carbon (9.5 g) to the clear solution at 65-67°C with stirring for 1 hour at 65-67°C. Filtered the reaction mass while hot under vacuum through celite bed at 65-67°C. Washed the celite bed with tetrahydrofuran (190 ml). Recovered the solvent under vacuum at 50-55°C leaving behind about 78 ml of the reaction mass. The resultant suspension was cooled under stirring slowly to 35°C and maintained for further 30 minutes. Further cooled to 3-5°C and maintained for 2 hours under stirring at 3-5°C.

The solid separated were filtered and the wet cake was slurry washed with isopropyl alcohol (285 ml). The product was then dried under vacuum at 50-55°C for 7-8 hours till the moisture is less than 0.5 % w/w.

Yield: 67 g (71%)
Purity : greater than 99.75% by HPLC
Impurity: Total impurities not more than 0.25% by HPLC

EXAMPLE 4

PREPARATION OF SUBSTANTIALLY PURE ZIPRASIDONE HYDROCHLORIDE

To substantially pure ziprasidone base (100 g) was added dichloromethane (2.0 Lit) and stirred for 15-20 minutes at 30-35°C. To the mixture added ethereal solution of hydrogen chloride (95.7 ml) over a period of 5-10 min at 30-35°C under stirring. The suspension was further stirred for 17-20 hours at 32-35°C and separated solids were filtered under vacuum and nitrogen atmosphere at 32-35°C. Wet solid were washed with diethyl ether (100 ml). The wet cake was suspended in acetone (500 ml) at 30-35°C and stirred for 15-20 minutes at 30-35°C. Filtered the solids and washed wet cake with acetone (0.20 Lit) and dried under vacuum at 55-60°C for 12-15 hours till the moisture content is not more than 0.5 % w/w.

Yield: 105 g (94%)
Moisture content by Karl Fischer: Less than 0.5 % w/w
Purity: greater than 99.9 % by HPLC.
Impurity: Total impurities not more than 0.1% by HPLC

Dated this **26TH** day of **February, 2004.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

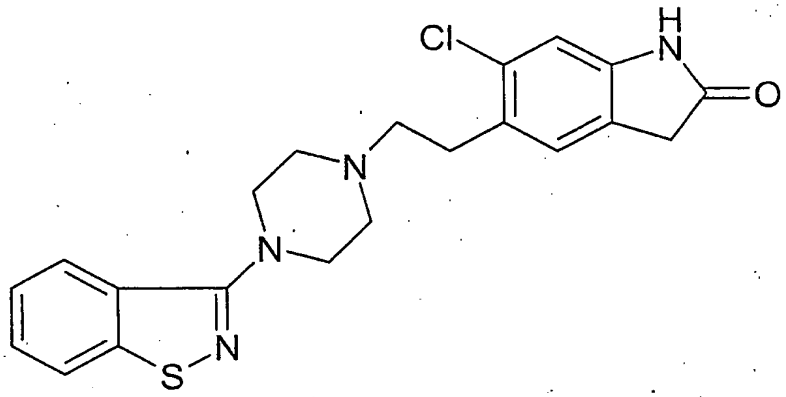
Application No.

No. of sheets = 03

Sheet 01 of 03

0707-04

27 FEB 2004



FORMULA IA: HCl SALT

FORMULA IB: FREE BASE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

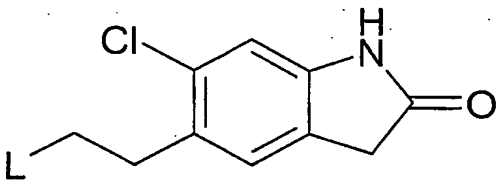
Application No.

No. of sheets = 03

Sheet 02 of 03

0707-04

27 FEB 2004



FORMULA II

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

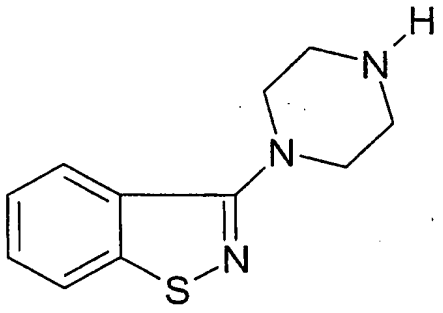
Application No.

No. of sheets = 03

Sheet 03 of 03

687-04

27 FEB 2004



FORMULA III

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)

Company Secretary

ABSTRACT

PROCESS FOR PREPARATION OF BENZOISOTHIAZOLE PIPERAZINE DERIVATIVES OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

The present invention relates to a process for preparation of benzoisothiazole piperazine derivative or a pharmaceutically acceptable salt thereof. The present invention also relates to substantially pure benzoisothiazole piperazine derivative or a pharmaceutically acceptable salt thereof.